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EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 11/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,317	RASMUSSEN ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *30,31 and 35-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, represented by claims 1-29 and 32-34, in the reply filed on August 23, 2006 is acknowledged.

Claims 30, 31, and 35-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 23, 2006.

Accordingly, claims **1-29** and **32-34**, to the extent they are drawn to a method for *in vivo* down-regulation of amyloid precursor protein (APP) or beta amyloid (Aβ), comprising administering a polypeptide analogue of APP or Aβ, are under examination in the instant office action.

Information Disclosure Statement

A signed and initialed copy of the IDS paper submitted March 21, 2005 is enclosed in this action. It is noted that one page of the submitted IDS has been crossed out as the references are duplicated in whole.

Priority

Acknowledgement is made of Applicant's claim for foreign priority. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The disclosure is objected to because of the following informalities: typographical errors have been noted at: p. 1, line 7 for "Sugust"; p. 97, line 8 for "tabel"; and p. 99, line 7 for "croos-linked". Applicant is reminded to thoroughly check the disclosure for other such errors.

Appropriate correction is required.

Claim Objections

Claim 10 is objected to because of the following informalities: there appears to be a typographical error in the word "hemagluttinin", which should be spelled "hemagglutinin". Appropriate correction is required.

Claim 27 is objected to because of the following informalities: the word "sublinqual" appears to be spelled incorrectly. Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-29, 32 and 34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-21, 24-25 and 42 of copending Application No. 10/223,809 ('809). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '809 application contains claims drawn to a method for *in vivo* down-regulation of amyloid precursor protein (APP) or beta amyloid (Aβ) in an animal, such as a human, by immunizing the animal with an analogue of APP or Aβ that contains at least one B-cell epitope of APP or Aβ and one foreign T helper epitope (claim 1 of '809) and a method for treating and/or preventing and/or ameliorating Alzheimer's disease or other diseases and conditions characterized by amyloid plaques (claim 25 of '809), which are not patentably distinct from the instantly claimed methods (such as in instant claims 1 and 34). Further, nearly identical dependent limitations, with minor variations, are recited in

each claim set in each of the applications. For example, claim 28 of the instant application recites intracutaneous, subcutaneous, and intramuscular routes of administration, whereas claim 19 of the '809 application recites multiple administration routes, including the intramuscular route among others, and claim 20 of '809 recites intracutaneous or subcutaneous administration. Accordingly, the claims of copending application '809 would render obvious instant claims 1-29, 32 and 34.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 6-13, 23, 25-28, and 32-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9, 10, 25, 26, 33, 59, 60, 65-68, 71, 72, 74, 75, 78 and 83 of Application No. 09/785,215, which claims have recently been allowed as U.S. Patent No. 7,135,181 and renumbered as 7-13, 17-20, 1-5 and 24, respectively (in total, claims 9, 10, 25, 26, 33, 59, 60, 62-69, 71, 72, 74, 75, 78, 79 and 81-83 of the '215 application were allowed). The Examiner notes that the patent has not yet been printed. For the sake of clarity, the claim numbers recited in this rejection are in reference to the renumbered claims of the '181 patent and not the original claim numbers of the '215 application. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '181 patent contains claims drawn to a method for reducing amyloid plaque burden in a mammal which particular recited species would render obvious the instantly recited method for *in vivo* down-regulation of amyloid precursor protein (APP) or beta

amyloid (Aβ) in an animal (instant claim 1), wherein the method is used for treatment of Alzheimer's disease or other diseases characterized by amyloid deposits (as in instant claim 34). The methods of the '181 patent and the instant application both recite immunization of an animal with an Aβ or APP polypeptide (i.e., an Aβ or APP analogue, as recited in the instant claims) which has been modified by insertion of at least one foreign T helper epitope into the Aβ or APP sequence (i.e., disruption of said sequence so that the analogue does not have any T cell epitopes of its own). Although the '181 patent does not specifically recite that the modified Aβ or APP polypeptide "incorporates into the same molecule a substantial fraction of B-cell epitopes of APP and/or Aβ so that the [polypeptide] reacts to the same extent as does APP or Aβ with a polyclonal serum raised against APP or Aβ", as recited in instant claim 1, the modified Aβ or APP polypeptide of the '181 patent would nevertheless inherently possess such B-cell epitopes in its sequence and thus would also be expected have the desired property of reacting with (i.e., being recognized and bound by) polyclonal Aβ/APP serum antibodies. Additionally, the recitation in instant claim 12 that the analogue "comprises B-cell epitopes which are not exposed to the extracellular phase when present in a cell-bound form of the precursor polypeptide Aβ" would be rendered obvious by, for example, claim 5 of the '181 patent which recites the species of a modified Aβ or APP polypeptide comprising amino acids 672-714 of SEQ ID NO: 2 wherein an isolated foreign T helper epitope has been introduced by means of insertion. The extracellular portion of Aβ/APP (SEQ ID NO: 2) includes residues 672-700, and thus B-cell epitopes which are not exposed can be found in residues 701-714 of SEQ ID NO: 2, which are

normally found in the transmembrane portion of Aβ/APP. Similarly, the Aβ analogue species recited in claim 24 of the '181 patent (including residues 729-734 of SEQ ID NO: 2, which is intracellular) would render obvious the analogue of instant claim 13. Further, both claim 1 of the '181 patent and claim 1 of the instant application recite that the administration (i.e., immunization) of the modified Aβ/APP polypeptide (i.e., the Aβ/APP analogue) to the animal induces production of antibodies against the animal's autologous APP or Aβ.

Further, identical claimed limitations, or obvious variations thereof, exist in both the '181 patent claims and the instant claims. For example, the method of the '181 patent further recites that the foreign T helper epitope is selected from the group consisting of a Tetanus toxoid epitope, a diphtheria toxoid epitope, an influenza virus hemagglutinin epitope, a *P. falciparum* CS epitope and an artificial MHC-II binding peptide sequence (claim 1 of '181), wherein the foreign T-cell epitope is selected from a natural promiscuous T-cell epitope and an articificial MHC-II binding peptide sequence (claim 12 of '181), wherein the foreign T-cell epitope is immunodominant in the mammal (claim 7 of '181) and wherein it is promiscuous (claim 8 of '181), and wherein the tetanus toxoid epitope is selected from SEQ ID NO: 4 (P2) and SEQ ID NO: 6 (P30) (claim 13 of '181), thus rendering obvious instant claims 7-11. Limitations in the '181 patent such as linkage of the analogue to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants (claim 9), formulation with an adjuvant to facilitate breaking of autotolerance to autoantigens (claim 10), the number of administration per year (claims 11, 18 and 19), parenteral administration by

subcutaneous, intracutaneous, or intramuscular routes (claim 20), recitation of first, second and third moieties of the analogue (claim 2) wherein, for example, the first moiety is a specific binding partner selected from a hapten and a carbohydrate and the third moiety is selected from a lipid and a polyhydroxypolymer (claim 2), and wherein in polyhydroxypolymer is a polysaccharide (claim 17), thus rendering obvious instant claims 3, 6, 23, 25, 26-28, 32 and 33. Accordingly, the claims of the '181 patent would render obvious instant claims 1, 3, 6-13, 23, 25-28 and 32-34.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 and 32-34 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing amyloid plaque burden in an animal model of Alzheimer's disease, such as transgenic amyloid precursor protein (APP) mice, by administration of an Aβ polypeptide analogue comprising at least residues 672-683 of SEQ ID NO: 2 (APP) (amino acid residues 1-12 of Aβ) or by administration of an Aβ polypeptide analogue that contains at least one foreign T helper epitope and a disrupted APP or Aβ sequence so that the analogue does not include any subsequence of SEQ ID NO: 2 that binds productively to MHC class II molecules initiating a T-cell response, does not reasonably provide enablement for a method for down-regulation of APP or Aβ in an animal, such as a human, or for treating and/or

preventing and/or ameliorating Alzheimer's disease or other diseases or conditions characterized by amyloid deposits by immunizing the animal/human with all analogues of APP/Ab containing at least one B-cell epitope of APP/Aβ and at least one T_H epitope to induce production of antibodies against the animal's autologous APP/Aβ as broadly claimed. The specification is also enabling for a method of producing high titers of polyclonal anti-Aβ antibodies comprising administering to an animal a construct comprising (1) an Aβ polypeptide analogue that comprises at least residues 672-683 of SEQ ID NO: 2 (APP) (amino acid residues 1-12 of Aβ), and (2) at least one foreign T helper epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claims are broadly drawn to an *in vivo* method for down-regulation of amyloid precursor protein (APP) or beta amyloid (Aβ) in an animal, such as a human, comprising immunizing the animal with at least one analogue of APP or Aβ containing at least one B-cell epitope of APP/Aβ and at least one foreign T-helper epitope to induce the production of antibodies against APP or Aβ, with dependent claim 34 reciting that

the down-regulation method is used for treating and/or preventing and/or ameliorating Alzheimer's disease or other diseases and conditions characterized by amyloid deposits, where APP or Aβ is down-regulated to such an extent that the total amount of amyloid is decreased or that the rate of amyloid formation is reduced with clinical significance.

The nature of the invention is the demonstration that administration of a modified Aβ polypeptide construct comprising APP/Aβ analogue polypeptide sequences and T helper epitopes to transgenic APP mice leads to greatly enhanced serum titers of anti-Aβ42 specific antibodies compared to mice administered wild-type $A\beta_{1-42}$ polypeptide alone (see Example 2, in particular). Applicant additionally shows that the amount of modified construct required to achieve the enhanced production of antibodies was only half as much as the wild-type $A\beta_{1-42}$ sequence used for immunization.

The state of the art acknowledges that immunization with Aβ leads to beneficial results in transgenic animal models of Alzheimer's disease (AD), but that many issues still need to be resolved in immunotherapy of AD in humans (for a review, see De Felice and Ferreira, *Cell Mol Neurobiol.* 2002; 22(5-6): 545-563). Applicant's invention is predicated on prior art showing that administration of $A\beta_{1-42}$ peptide to PDAPP transgenic mice, which overexpress mutant human APP and progressively develop many of the neuropathological hallmarks of Alzheimer's disease (AD), leads to a reduction in amyloid plaque formation, neuritic dystrophy, and astrogliosis (Schenk et al. *Nature*, 1999; 400: 173-177). Additionally, it has been shown that administration of $A\beta_{42}$ to other transgenic (Tg) murine models of AD (TgCRND8 and Tg2576+PS1 mice, for

example) leads to reductions in both cognitive dysfunction and memory impairments in aged Tg mice (see Janus et al. *Nature*, 2000; 408: 979-982; Morgan et al. *Nature*, 2000; 408: 982-985). De Felice et al. (2002) notes that the exact mechanism by which Aβ immunization achieves these improvements is not fully understood, and may include anti-Aβ antibody-mediated clearance and/or inhibition of Aβ aggregation, microglial phagocytosis of Aβ, and/or the redistribution of Aβ from neuritic plaques to diffuse plaques. However, although Aβ peptide immunization has been shown to be effective in transgenic murine models of Alzheimer's disease, clinical trials using Aβ peptide vaccines in AD patients have revealed serious negative side effects of the immunotherapy in a number of the patients, such as inflammation of the CNS, which is indicative of a potential breakdown of the blood-brain barrier and entry of T-cells into the brain (see p. 551 of De Felice et al. 2002; and Münch and Robinson, *J Neural Transm*, 2002; 109: 1081-1087). The art to which the present invention relates is therefore highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy. Thus, the state of the prior art can be characterized as (1) recognizing that immunization of transgenic Aβ or APP mice with Aβ42 can reduce brain amyloid deposits and improve memory deficits, (2) not fully comprehending the mechanism by which immunization with Aβ works, (3) recognizing that animal models of Alzheimer's disease are not predictive of the true human disease, and (4) acknowledging that immunotherapeutic treatment of Alzheimer's disease in humans is unpredictable.

Applicant extrapolates the prior art findings to assert that administration of a more immunogenic Aβ peptide analogue will induce greater antibody responses and thus provide for down-regulation of APP/Aβ and thus for treatment and/or prevention and/or amelioration of AD or other diseases characterized by amyloid beta deposits, particularly in humans. However, no guidance, prophetic or otherwise, is provided demonstrating that administration of the claimed APP/Aβ analogues to an animal or human effectively results in the treatment or prevention or amelioration of Alzheimer's disease. Additionally, Applicant fails to provide sufficient guidance as to whether all analogues of APP/Aβ that contain a substantial fraction of B-cell epitopes of APP and/or Aβ and any at least one foreign T_H epitope can be used to down-regulate APP/Aβ in an animal, including a human. The specification further lacks guidance as to whether analogues comprising B-cell epitopes not normally exposed extracellularly (or else lacking at least one extracellular B-cell epitope) or analogues wherein the particular APP sequence is not specified and can include intracellular only portions of APP/Aβ, such as particular analogues recited in claims 12-22, are able to induce a sufficient immune response to down-regulate APP/Aβ. The art teaches that Aβ peptides not containing N-terminal residues of Aβ (particularly residues 1-5 of Aβ) are poor immunogens and are not capable of reducing brain Aβ deposits in transgenic PDAPP mice (see Schenk et al., WO 99/27944, particularly pp. 51-57). Additionally, as is noted above, the prior art provides only for teachings of reduction of fibrillar Aβ and deposited Aβ aggregates, and does not in any case teach the down-regulation or reduction of the precursor protein APP. The specification provides no guidance or evidence of *in vivo*

down-regulation of APP. It would thus require undue experimentation to use all possible analogues of APP/Aβ peptides in an immunization method to effect an immune response – without adverse inflammatory effects in the CNS – and to successfully down-regulate APP or Aβ or provide treatment/prevention/amelioration of Alzheimer's disease or other amyloid-associated diseases.

Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the particular claimed analogues are able to reduce Aβ levels within the brains of human Alzheimer's patients, and in no way demonstrates prevention of Alzheimer's disease.

The art also recognizes that Alzheimer's disease has many features, including short-term memory loss, behavioral abnormalities, as well as a multitude of anatomical abnormalities such as the presence of both amyloid plaques and neurofibrillary tangles. See for example Small et al. *Proc Natl Acad Sci USA*, 2000; 97:6037-6042. Additionally, Alzheimer's disease is characterized by changes in permeability of the blood brain barrier; see Anderson (U.S. Patent 5,589,154), particularly column 6 lines 27 - 40, where the reference teaches that beta-amyloid protein, the causative agent in Alzheimer's diseases, also induces vascular damage. Applicant fails to provide guidance on the treatment of these other features associated with Alzheimer's disease pathology, which would be encompassed by treatment of AD. Moreover, both at the time of filing and now, effective therapy for the prevention of Alzheimer's has eluded

researchers. De Lustig et al. (*Rev in Neurosciences*, 1994, 5: 213-225) report that there is still no adequate preventive strategy and no effective therapies for the pathology, and the disease thus follows an inevitable degenerative course. And a recent review by Vickers (*Drugs Aging*, 2002, 19(7): 487-494) notes that there is no effective treatment currently available to reverse, slow down or prevent the course of Alzheimer's disease and most other brain diseases and conditions.

Additionally, the art recognizes that amyloid is a generic term referring to a group of diverse, but specific extracellular proteins and protein deposits which have common morphological characteristics (see US Patent 6,340,783 B1 to Snow). Snow notes that although amyloid deposits in all clinical conditions share common physical properties relating to the presence of a beta-pleated sheet conformation, it is now clear that many different chemical types exist which are totally structurally unrelated, such as serum amyloid A (SAA), serum amyloid P component (SAP), AL amyloid (variable region of light chain immunoglobulin), transthyretin, $beta_2$-microglobulin, procalcitonin. Further, there are many conditions and diseases associated with each of these amyloids, each with it own unique etiology. Moreover, the art recognizes that it is unpredictable as to whether immunotherapy directed to one of these amyloid proteins would be capable of effecting treatment in a disease characterized by a completely different amyloid protein. For example, Janus et al. (2000) show that immunization of transgenic APP mice with islet-associated polypeptide (IAPP), which has similar biophysical properties to Aβ but is associated with a non-central nervous system amyloidosis, was incapable of reducing Aβ plaque area in the brains of the mice (see Figure 3 in particular). The instant

specification provides no guidance as to the treatment of other diseases and conditions characterized by amyloid deposits. Thus, it would require undue experimentation to use the APP/Aβ analogues in a method of treating/preventing/ameliorating diseases or conditions characterized by amyloid deposits other than Alzheimer's disease.

Furthermore, even assuming *arguendo* that the specification was enabling for a method of treating/preventing/ameliorating Alzheimer's disease, it would still not be enabled for a method of treating/preventing/ameliorating Alzheimer's disease using the full scope of APP/Aβ analogues for the reasons set forth above.

Therefore, in view of the breadth of the claims encompassing compositions comprising an indeterminate number of peptide analogue constructs, production of antibodies to these compositions and therapeutic and preventative methods using the compositions to a genus of amyloid-associated diseases, the lack of adequate guidance or working examples on the use of the peptide constructs for down regulation of APP/Aβ and/or immunotherapy, the lack of sufficient guidance or data or evidence supporting a preventative effect of the claimed analogues, or guidance on their use, the unpredictability in the art of treatment of Alzheimer's disease, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

Claims 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite three "moieties". The first moiety effects the targeting of the analogue to an antigen presenting cell (APC) or a B-lymphocyte, the second moiety stimulates the immune system, and the third moiety optimizes presentation of the analogues to the immune system. However, as each of these moieties are not limited by structural definitions and encompass a vast genus of molecules, and therefore are genus claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. Factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. (Written description guidelines, Federal Register, vol. 66, no. 4, January 2002, 9.1106, column 2). In the instant case, the only factor present in the claims that is sufficiently disclosed for the "moieties" is the desired functional property for each moiety. The scope of the claims includes numerous moieties potentially capable of effecting targeting, stimulating the immune system, or optimizing presentation of the immunogen, and the genus for each of these is highly variable because a significant degree of structural variation is permitted. The specification does not identify any particular portion of the structure of each of these

moieties that must be conserved to elicit the desired response, nor does it provide a disclosure of structure/function correlation. Structural features that could distinguish the instantly claimed moieties in the genus from any other compound or material are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Given the fact that the specification does not provide sufficient examples for each of the first, second, and third moieties that are species of the claimed genus of moieties capable of effecting targeting, stimulating the immune system, or optimizing presentation of the analogue, respectively, and the lack of guidance on the common structural attributes or characteristics that would aid in the identification other members of the genus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "substantial fraction of B-cell epitopes" in claim 1 is a relative phrase which renders the claim indefinite. The term "substantial" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what constitutes a "substantial" fraction of B-cell epitopes is not unambiguously defined by the specification or the prior art.

Claims 2-29 and 32-34 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for being dependent from indefinite rejected claim 1.

The term "optimizes" in claim 3 is a relative term which renders the claim indefinite. The term "optimizes" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Applicant fails to set forth the metes and bounds of what is encompassed within the definition of "optimizes". Since the specification and the prior art do not define the metes and bounds of the term, the skilled artisan would not be able to determine what measure or outcome constitutes optimization of presentation to the immune system. The claim is thus indefinite.

The term "precursor polypeptide Aβ" in claim 12 is an ambiguous term which renders the claim indefinite. The term "precursor polypeptide Aβ" is ambiguous and confusing because APP (amyloid precursor protein) is the precursor polypeptide from which the product amyloid beta (Aβ) is derived. Therefore, it is not clear if Applicant

means APP or Aβ in this instance. The metes and bounds of the claim thus cannot be ascertained.

Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the time unit of the frequency of administration/introduction. The claim recites at least 2, 3, 4, 6, or 12 administrations/introductions but does not indicate what the time unit of the administrations is, i.e. per year, per month, per week, etc. The metes and bounds of the claim thus cannot be ascertained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-23, 26-29 and 32-34 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/27944 by Schenk, published June 10, 1999, as evidenced by Panina-Bordignon et al. (*Eur J Immunol. 1989*; 19: 2237-2242, as listed on Applicant's IDS).

The instant claims are drawn to a method for the *in vivo* down-regulation of amyloid precursor protein (APP) or beta amyloid (Aβ), comprising immunizing an animal with an analogue, wherein the analogue (1) is a polypeptide that contains at least one foreign T_H epitope and a disrupted APP or Aβ sequence of SEQ ID NO: 2, and/or (2) is a conjugate comprising a polyhydroxypolymer back to which is coupled the polypeptide of (1), and/or (3) is a conjugate comprising a polyhydroxypolymer backbone to which is separately coupled at least one foreign T_H epitope and a polypeptide as in (1). Additional claim limitations will be noted throughout the body of the rejection below. For clarity's sake, the Examiner notes that SEQ ID NO: 2 is the amino acid sequence for APP and is recognized in the art and the instant specification to consist of 770 amino acid residues. Aβ is derived from APP, and comprises residues 672-714 of APP for the Aβ42 variant, residues 672-712 of APP for the Aβ40 variant, etc. Briefly, when present in a cell-bound form, the extracellular portion of APP is residues 1-700 (comprising residues 1-28 of Aβ); the transmembrane portion of APP is residues 701-723 (comprising residues 29-42 of Aβ42); and the intracellular portion of APP is residues 724-770.

Schenk teaches a method of reducing Aβ plaque burden in the brains of transgenic PDAPP mice (made to overexpress human APP) by immunization with compositions comprising Aβ peptide and variants thereof, analogs and mimetics of Aβ peptide, and APP derivatives, see in particular p. 13-15 and Figures 3, 4, 7, 8, 11 and 12. Immunization with the Aβ peptide immunogens is demonstrated to induce the production of anti-Aβ antibodies in the animals (see Figures 5, 6 and 13). Schenk also

discloses a method of treating a disease characterized by amyloid deposition in a patient, such as Alzheimer's disease (see p. 3, lines 2-17), thus meeting a limitation of instant claim 34. The Aβ peptides are disclosed as including immunogenic fragments having a sequence of at least 3, 5, 6, 10 or 20 contiguous amino acids, such as Aβ1-5, 1-6, 1-12, 13-28, 17-28, 25-35, 35-40 and 35-42 (see p. 15), thus meeting recited limitations of instant claims 12-22 for specific non-extracellular B-cell epitopes (see above) and sequence lengths. The immunogenic agents include natural Aβ peptides, active fragments and analogs of natural Aβ peptides, exhibiting at least 80-90% sequence identity with natural peptides, wherein the peptides contain an epitope (i.e., a B- or T-cell epitope) that induces protective or therapeutic immune response upon administration (see p. 11 and 15). Schenk also teaches compositions comprising Aβ or active fragments thereof linked to a conjugate/carrier molecule that promotes delivery of Aβ to the bloodstream of a patient and/or promotes an immune response against Aβ (see p. 4, lines 34-37. Suitable carriers include tetanus toxoid, or a toxoid from other bacteria such as diphtheria, *E. coli*, cholera, or *H. pylori*, and can also include carriers for stimulating or enhancing an immune response such as cytokines and chemokines (see p. 20, lines 1-10). Further, tetanus toxoid would comprise natural promiscuous T-cell epitopes, such as P2 and P3, which are immunodominant in an animal, as evidenced by Panina-Bordignon et al. (see p. 2241 in particular). Accordingly, these teachings would anticipate recited limitations of instant claims 3 and 7-11. Additionally, the use of immune-stimulating carriers, such as tetanus toxoid, would be expected to

inherently enhance the immune response sufficiently enough to facilitate breaking of autotolerance to autologous Aβ antigens, thus meeting a limitation of instant claim 26.

Schenk teaches that the Aβ peptides can be linked to the carriers by chemical crosslinking via, for example, disulfide-amide linkage between the peptide and the carrier (see p. 20, lines 13-32), thus anticipating a recited limitation of instant claim 4. The immunogenic Aβ peptides can also be expressed as fusion proteins with carriers, wherein the immunogenic peptide can be linked to the carrier at the amino terminus, the carboxyl terminus, or internally within the immunogenic peptide sequence, and wherein multiple repeats of the immunogenic peptide can be present in the fusion protein (see p. 20, lines 33-37), thus meeting recited limitations of instant claims 5, 6 and 23.

Schenk discloses that the dose of immunogen (i.e. Aβ peptide) administered to the patient, such as a human, varies from 1 μg to 500 μg per patient, wherein a higher dose of 1-2 mg (1000-2000 μg) may occasionally be used (see p. 3, lines 24-27 and p. 24, lines 15-20), thus meeting recited limitations of instant claims 2 and 29. The timing of injections is disclosed to vary from once a day, to once a year, to once a decade, but a typical regimens consist of an immunization followed by booster injections at: 1) 6 weekly intervals, or 2) at 1, 2 and months, or 3) at two month intervals (see p. 24, lines 26-32), thus meeting the limitations of instant claims 32 and 33. The disclosed routes of administration include: parenteral, intranasal, intravenous, oral, subcutaneous, intraperitoneal, topical, intramuscular, intracranial, and intradermal administration (see p. 25, lines 3-15), as well as formulations suitable for oral, intranasal, pulmonary, suppository, and transdermal application (see p. 29, lines 15-17), which would thus

anticipate the recitations of instant claims 27 and 28. Accordingly, the document by Schenk anticipates instant claims 1-23, 26-29 and 32-34

Claims 1-23, 27-29 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 01/42306 A2 by Chain, published June 14, 2001, priority to December 8, 1999, as evidenced by Panina-Bordignon et al. (*Eur J Immunol.* 1989; 19: 2237-2242, as listed on Applicant's IDS).

The claims are drawn to *in vivo* down-regulation of APP/Aβ and treatment methods as noted above.

Chain discloses chimeric peptides or mixtures of chimeric peptides that can be formulated as an immunizing composition and used in a method for immunization of a mammal against amyloid beta or APP (see Abstract and p. 1). The chimeric peptide immunogen comprises a B cell epitope from a naturally-occurring internal peptide cleavage product of a precursor or mature protein (i.e. Aβ) joined with or without spacer amino acid residues to a T helper cell epitope derived from a different source. For example, Chain teaches immunization with a chimeric peptide(s) containing an Aβ end-specific B cell epitope and a promiscuous T helper cell epitope of tetanus toxoid as a preferred embodiment, which would give rise to Aβ antibodies for inhibiting, reducing or even reversing Aβ deposit/plaque formation (see p. 10, lines 18-22 and 32-36). One such T helper epitope of tetanus toxin disclosed by Chain is the P2 epitope (SEQ ID NO: 8, see p. 3 of sequence listing), which is known in the art to be immunodominant, as evidenced by Panina-Bordignon et al., thus anticipating instant claims 7 and 11. In

addition to tetanus toxoid epitopes, Chain teaches the use of other promiscuous T helper cell epitopes derived from diphtheria toxin, *P. Falciparum* CS, measles virus F protein, and pertussis toxin among others (see pp. 15-17), thus anticipating instant claims 8-10.

Regarding the amyloid peptide sequences, Chain teaches that the B-cell epitope can be from the N- or C-terminus of Aβ and can be as few as 2-5 amino acid residues in length (see pp. 13-14), thus anticipating instant claims 14-22. Such C-terminal sequences of Aβ (such as SEQ ID NO: 7, see claim 3, p. 34) would comprise B-cell epitopes which are not exposed to the extracellular phase when present in a cell-bound form of APP, or in other words, C-terminal Aβ sequences would lack at least one B-cell epitope which is exposed to the extracellular phase when present in a cell-bound form of APP, thus meeting recited limitations of instant claims 12-13. Chain further discloses that the chimeric peptide can include mixtures of N- and/or C-terminal Aβ peptides joined to T helper epitopes (see p. 13, lines 17-27), which means that duplicate or multiple copies of at least one B-cell epitope of Aβ would be present in the chimeric peptide, thus anticipating instant claim 6. Chain teaches that the chimeric protein can be produced recombinantly as a fusion polypeptide (see p. 9, line 13 and p. 19, lines 19-34), thus anticipating instant claim 5. Chain also discloses that an immunoeffective amount of the chimeric peptide can be 0.5 μg to 1 mg per kg body weight (see p. 24, lines 11-17), which would anticipate instant claim 29. The immunizing composition is taught to be administered by any convenient route including subcutaneous, oral,

intramuscular, or other parenteral or internal route (see paragraph spanning p. 23-24), which would anticipate instant claims 27 and 28.

Chain also discloses coupling additional immunostimulatory molecules to the chimeric peptide covalently (as in the case of integrin domains, for example) or non-covalently (as in the case of adjuvants), see pp. 19-21, which would anticipate the coupling of targeting, and/or stimulatory, and/or optimizing "moieties" of instant claims 3 and 4. Moreover, linkage of the chimeric peptide, which may comprise more than one N- or C-terminal Aβ peptide fragment (as discussed above), to such carrier molecules would anticipate instant claim 23.

Finally, Chain teaches the use of adjuvants with the chimeric peptides to enhance immunogenicity (see p. 21-22), thus meeting a recited limitation of instant claim 26. Chain additionally comments that chimeric peptides comprising non-self T cell epitopes are advantageous because they facilitate breaking self-tolerance, which allows for the production of antibodies to the self-antigen (see p. 12, lines 20-22). Accordingly, the immunization method disclosed by Chain would anticipate the method for *in vivo* down-regulation of Aβ or APP in a mammal, and also the method for the treatment of Alzheimer's disease of instant claims 1 and 34 (see, for example, p. 4 wherein Chain discusses therapeutic reduction of the amount of amyloid deposits in the CNS, particularly in Alzheimer's disease). Because Alzheimer's is a uniquely human disease, Chain's disclosure encompasses treatment of human beings, as recited in instant claim 2. Thus, the document by Chain anticipates instant claims 1-23, 27-29 and 34.

Claims 1-29 and 32-34 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 7,135,181 by Jensen et al., issuance date of November 14, 2006, effective filing date of March 1, 2000. Because the patent has not been printed as of the date of this office action, the recited page and line numbers are in reference to the non-provisional US application of the '181 patent, Application No. 09/785,215 (US 2002/0187157).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The teachings of the allowed claims of the '181 patent are discussed above (see obviousness-type double patenting rejection). As noted above, the teaching of limitations in instant claims 1, 3, 6-13, 23, 25-28, and 32-34 would be met. In summary, Jensen et al. teach a method for reducing amyloid plaque burden in a mammal, including a human being (see [0055]), via immunization with a modified Aβ or APP polypeptide comprising at least one foreign T helper epitope inserted into the Aβ or APP sequence, thus anticipating instant claim 2. In addition, Jensen et al. teach that such modified APP/Aβ polypeptides as a conjugate comprising coupling the polypeptide to a polyhydroxypolymer backbone via an amide bond (see [0126-0127]), thus anticipating instant claim 24. Jensen teaches that side groups, such as foreign T helper epitopes

and the first, second and third moieties recited in instant claim 3, for example, may be covalently or non-covalently attached to the amyloid polypeptide (see [0120-0125]), thus meeting a recited limitation of instant claim 4. Jensen also teaches that the APP/Aβ/T helper epitope conjugate may be a fusion polypeptide (see [0094]), thus anticipating instant claim 5, and further discloses particular sequences of SEQ ID NO: 2 conducive to conjugate formation (see [0132-0133]) which would anticipate the recited limitations of instant claims 14-22. Finally, Jensen discloses effective amounts of the APP/Aβ analogue that would anticipate instant claim 29 (see [0139]). Therefore, the newly issued patent by Jensen et al. anticipates instant claims 1-29 and 32-34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-29 and 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/27944 by Schenk, published June 10, 1999, as evidenced by Panina-Bordignon et al. (*Eur J Immunol.* 1989; 19: 2237-2242, as listed on Applicant's IDS), and in view of Lees et al. (*Vaccine*, 1994; 12(13): 1160-1166).

The teachings of Schenk are discussed *supra*. Briefly, Schenk teaches Aβ peptide immunogens, which contain B cell epitope(s), coupled to carrier molecules such as tetanus toxoid, which contain T helper epitopes. Further, Schenk teaches that the pharmaceutical compositions comprising the Aβ immunogenic peptides can include large, slowly metabolized macromolecules such as proteins, polysaccharides, polyglycolic acids and copolymers, polymeric amino acids, amino acid copolymers, and lipid aggregates. Schenk discloses that these carriers can function as immunostimulating agents, (i.e. adjuvants), see p. 28, lines 20-27. Overall, Schenk provides numerous examples of agents to enhance the production of antibodies to Aβ peptides (see Examples VII-IX). However, while Schenk discloses the use of

polysacchrides as an immunostimulatory agent in general, Schenk does not specifically disclose that the Aβ immunogenic peptide analogs are coupled to a polyhydroxypolymer backbone.

Lees et al. disclose covalently coupling dextran, a polysaccharide which would comprise a polyhydroxypolymer backbone, to a protein to enhance the immunogenicity of the protein. Lees et al. teach that when a protein is coupled to dextran, a high-titre antibody response is elicited against the protein. Thus, the coupling of a protein to dextran would meet recited limitations in instant claims 1, 24 and 25.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to enhance the immunogenicity of the Aβ peptide analogs taught by Schenk by covalently coupling the peptide to the polysaccharide backbone of dextran, as taught by Lees et al. The skilled artisan would be motivated to make such modifications because Lees teaches that only small amounts of the proteins covalently coupled to dextran were necessary to induce significantly high titres of antibodies, and Lees additionally teaches that the antibody response persisted for at least four weeks. The skilled artisan would therefore also be motivated to make these modifications because, based on Lees teachings, fewer vaccinations with lower amounts of the dextran-coupled peptide would be necessary to achieve therapeutically effective antibody titres, and thus there would be a lowered risk of potential negative side effects associated with protein-based immunotherapy. The skilled artisan would further be motivated because enhancing antibody production in an individual with Alzheimer's disease, for example, would enhance the clearance of amyloid deposits, as indicated by

the work of Schenk. One of ordinary skill in the art would have expected reasonable success using the dextran-coupled Aβ immunogenic peptides to enhance the immunogenic response because Lees demonstrates that dextran-coupled peptides achieve much higher antibody titres than non-coupled peptides, and Schenk shows that antibodies produced against Aβ vaccinations were able to reduce amyloid plaques in the brains of transgenic PDAPP mice with higher antibody levels leading to greater clearance of amyloid deposits. Accordingly, the combined teachings of the references would render obvious instant claims 1-29 and 32-34.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
November 9, 2006

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SUPERVISORY PATENT EXAMINER